Research Article
Viral Hepatitis

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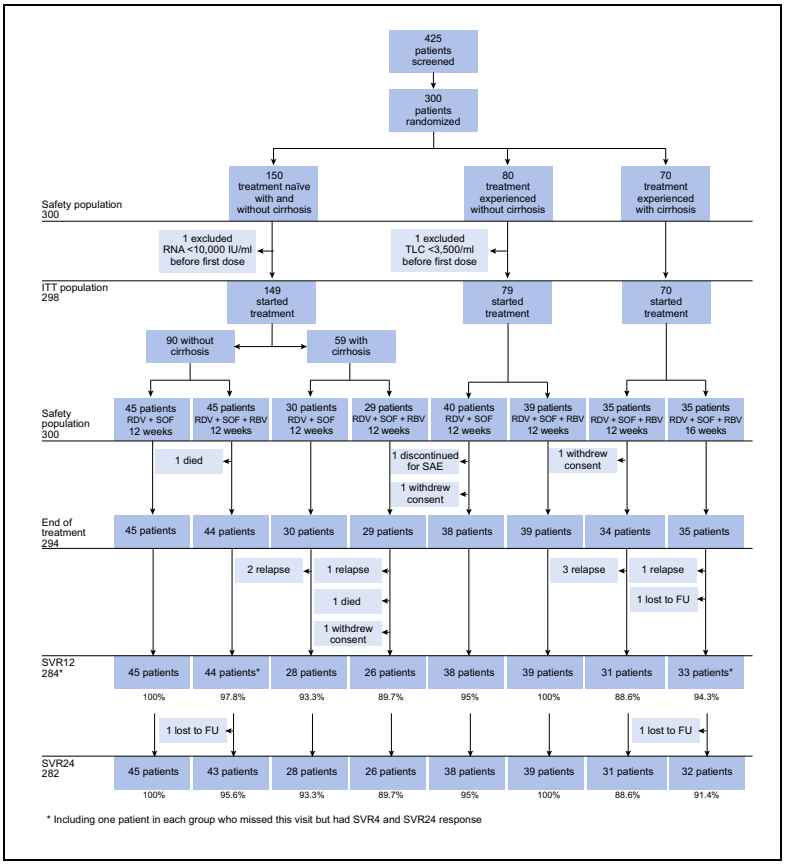
Effectiveness of ravidasvir plus sofosbuvir in interferon-naïve and treated patients with chronic hepatitis C genotype-4

Graphical abstract



Highlights

- Ravidasvir is a new NS5A inhibitor for HCV.
- Sofosbuvir + Ravidasvir with or without RBV has achieved very high SVR rates.
- Results are comparable for both patients with and without cirrhosis.
- Serious adverse events were noticed in very few treated patients.

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Lay summary

This study evaluated efficacy and safety of the new oral hepatitis C drug ravidasvir in combination with the approved oral drug sofosbuvir in 298 patients infected with hepatitis C type 4. Our results showed that treatment with ravidasvir plus sofosbuvir, with or without ribavirin, was well tolerated and associated with high response rate in patients with and without cirrhosis.

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Effectiveness of ravidasvir plus sofosbuvir in interferon-naïve and treated patients with chronic hepatitis C genotype-4

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Background & Aims: Although treatment of hepatitis C virus (HCV) and HCV-genotype-4 (GT4) has become very effective, it remains very expensive, and affordable options are needed, especially in limited resource countries. The aim of this study was to assess the efficacy and safety of the combination of ravidasvir (an NS5A inhibitor) and sofosbuvir to treat patients with chronic HCV-GT4 infection.

Methods: A total of 300 patients with HCV-GT4 infection were recruited in three groups: treatment-naïve patients with or without compensated Child-A cirrhosis (Group 1); interferon-experienced patients without cirrhosis (Group 2); and interferon-experienced patients with cirrhosis (Group 3). Groups 1 and 2 received ravidasvir 200 mg QD plus sofosbuvir 400 mg QD for 12 weeks and were randomized 1:1 to treatment with or without weight-based ribavirin. Group 3 patients received ravidasvir plus sofosbuvir with ribavirin and were randomized 1:1 to a treatment duration of 12 weeks or 16 weeks. The primary endpoint was sustained virologic response at 12 weeks post-treatment (SVR12).

Results: A total of 298 patients were enrolled: 149 in Group 1, 79 in Group 2 and 70 in Group 3. SVR12 was achieved in 95.3% of all patients who started the study, including 98% of patients without cirrhosis and 91% of patients with cirrhosis, whether treatment-naïve or interferon-experienced. Ribavirin intake and history of previous interferon therapy did not affect SVR12 rates. No virologic breakthroughs were observed and the study treatment was well tolerated.

Conclusions: Treatment with ravidasvir plus sofosbuvir, with or without ribavirin, was well tolerated and associated with high sustained virologic response rate for HCV-GT4 infected patients with and without cirrhosis, regardless of previous interferon-based treatments.

Trial Registration number: ClinicalTrials.gov Identifier: NCT02371408.

Lay summary: This study evaluated efficacy and safety of the new oral hepatitis C drug ravidasvir in combination with the approved oral drug sofosbuvir in 298 patients infected with hepatitis C type 4. Our results showed that treatment with ravidasvir plus sofosbuvir, with or without ribavirin, was well tolerated and associated with high response rate in patients with and without cirrhosis.

Introduction

Hepatitis C virus (HCV) infection is a major global health problem, affecting 70 million to 100 million people worldwide,[1] and accounting for around 360,000 deaths annually, owing to decompensated cirrhosis and hepatocellular carcinoma.[2] HCV-genotype-4 (GT4) accounts for 10%–15% of chronic HCV infection worldwide, affecting 12 to 15 million patients, mostly in limited resource countries in Africa and the Middle East. Egypt has the highest prevalence of chronic HCV worldwide; with genotype-4 the predominant genotype, present in more than 90% of affected patients.[3]

Treatment of HCV-GT4 with pegylated interferon (PEG-IFN) and ribavirin (RBV) resulted in sustained virologic response (SVR) rates of less than 50%.[4] Introduction of direct acting antiviral (DAA) therapies proved much more effective with better safety profiles.[5–11] Ravidasvir (RDV, formerly PPI-668) is a pan-genotypic NS5A inhibitor, with potent inhibitory activity against HCV-GT4, and was effective in phase I and II trials, where it inhibited replication of HCV variants that encoded known NS5A resistance mutations.[12–14] Sofosbuvir (SOF) is a pan-genotypic NS5B polymerase inhibitor. It serves as the backbone of many combination regimens, owing to its high efficacy, good safety profile and high barrier to resistance.[6]

There is still a need to develop effective interferon free direct acting oral antiviral therapies for HCV that are affordable in limited resource settings, where HCV-GT4 is one of the predominant genotypes. RDV has not been studied in the treatment of

Keywords: HCV; Ravidasvir; PPI-668; Sofosbuvir; Genotype-4; Sustained virologic response (SVR).
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HCV-GT4 patients, and was not previously studied in combination with SOF.

Herein, we present the results of a multicenter phase III trial that was designed to study the safety and efficacy of RDV in combination with SOF, with or without RBV in Egyptian patients with HCV-GT4.

Patients and methods

This was a randomized, open-label, multicenter, phase III study to assess the efficacy and safety of RDV plus SOF, with or without RBV, in patients with chronic HCV-GT4 enrolled at three clinical sites in Egypt.

Patients

We included male or female patients, 18 to 65 years of age, with chronic HCV-GT4 infection, with or without compensated Child-A cirrhosis, with serum HCV-RNA levels ≥10,000 IU/ml. Absence of cirrhosis was defined as a liver stiffness measurement less than 12.5 kPa by Fibroscan[15] or a screening liver biopsy indicating no cirrhosis. Presence of cirrhosis was defined as having a screening liver stiffness measurement equal to or more than 12.5 kPa by Fibroscan, or a liver biopsy at any time prior to screening showing presence of cirrhosis (Metavir fibrosis score 4 or Ishak score greater than 4). Patients were either treatment-naïve (had not received antiviral treatment for HCV previously) or treatment-experienced (previous non-responders to interferon-based therapy (interferon or pegylated interferon with or without ribavirin) whether they were null-responders, partial responders, or had relapsed after the end of therapy).

All patients signed an informed consent, and the study was conducted according to the International Conference of Harmonization guidelines, applicable regulations, and according to the Declaration of Helsinki. It was approved by the ethical committee of each center and the ethical committee of the Ministry of Health (approvals in supplementary material). The study was registered at ClinicalTrials.gov with Identifier: NCT02371408.

Exclusion criteria

Exclusion criteria included coinfection with HBV or HIV, mixed HCV genotypes, elevated alpha fetoprotein more than 100 ng/ml, uncontrolled diabetes (HbA1C higher than 8.5%), clinical or laboratory evidence or history of hepatic decompensation, or history of malignancy within the preceding 5 years. We also excluded patients with creatinine clearance less than 50 ml/minute or serum creatinine ≥1.5 times the upper limit of normal (ULN), serum albumin ≤3.2 g/dl for patients without cirrhosis or <3 g/dl for patients with cirrhosis, total bilirubin >2× times ULN, aspartate aminotransferase or alanine aminotransferase elevated more than 10 times ULN, international normalized ratio (INR) >1.5 for patients without cirrhosis or >2.0 for patients with cirrhosis, hemoglobin <11 g/dl for females and <12 g/dl for males, leukocyte count < 3,500/mm^3 or absolute neutrophil count <1,500/mm^3 or platelet count <75,000/mm^3 for patients without cirrhosis, and leukocyte count <3,000/mm^3 or absolute neutrophil count <1,200/mm^3 for patients with cirrhosis. Patients who had failed previous treatment with any DAA agents were also excluded.

Interventions

The study medications were RDV 200 mg tablets (Presidio Pharmaceuticals, Inc., San Francisco, California, USA) once daily, generic SOF 400 mg tablets (Pharco Pharmaceuticals, Amriya, Egypt) once daily, and RBV 200 mg capsules: 1,200 mg daily if the patient's weight was more than 75 kg, and 1,000 mg daily if the patient weight was less than 75 kg, given in two divided doses.

Patients were stratified into three groups according to previous treatment and the presence of cirrhosis:

- Group 1: no prior therapy for HCV, with or without cirrhosis.
- Group 2: treatment-experienced, without cirrhosis.
- Group 3: treatment-experienced, with cirrhosis.

Patients in Groups 1 and 2 were treated with RDV plus SOF for 12 weeks, and randomized 1:1 to receive RBV *vs.* no RBV. Patients in Group 3 received RDV plus SOF and RBV, and were

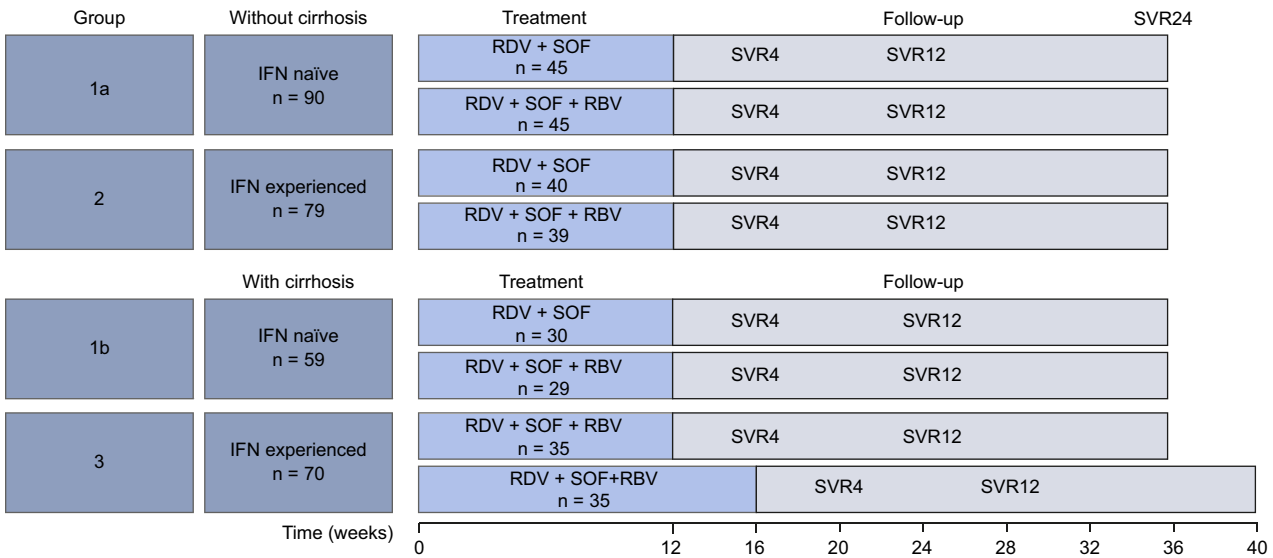

Fig. 1. Study design. IFN, interferon; RBV, ribavirin; RDV, ravidasvir; SOF, sofosbuvir; SVR12, sustained virologic response at 12 weeks post-treatment.

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randomized 1:1 to either 12-week or 16-week treatment duration (Fig. 1). Patients were randomized using a web-based system, and were treated and assessed in an un-blinded, open-label manner.

All patients were followed up for 24 weeks after the end of treatment. Vital signs were measured and samples were collected and stored at screening and on study visits on day 1, weeks 1, 2, 4, 8, and 12 (and 16, for group 3) and on post-treatment weeks 2, 4, 8, 12, and 24 for chemistry, hematology, viral load, and urinalysis. All study laboratory tests from all sites were performed at a central laboratory.

HCV-RNA was extracted from serum samples using Qiagen kit (Qiagen Inc., Valencia, CA, USA), and detected and quantified by reverse transcription PCR using real-time HCV assay (Abbott Molecular Inc., Des Plaines, Illinois, USA). The lower limit of quantification (LLOQ) was 12 IU/ml. Genotyping was performed by restriction fragment length polymorphism analysis of the nested PCR products.[16]

Sample size calculation

The sample size was calculated assuming historical response rates for Egyptian patients to peg-IFN-RBV therapy of 55% for treatment-naïve HCV-GT4 patients and 30% for retreatment of previous IFN non-responders. The postulated overall SVR rate for a patient population of 50% IFN-naïve and 50% IFN-experienced patients would be 43%. Assuming an SVR of at least 80% or more for the study regimens based on previous literature of similar treatment regimens (NS5A plus SOF, with or without RBV for HCV-GT4), and a two-sided alpha error of 5%, in order to reach a study power of more than 95%, a sample size of 300 patients was needed to demonstrate a superiority for RDV plus SOF therapy.

Study assessments

Analysis populations

- The safety population: all randomized subjects who received at least one dose of the study drugs were included in the safety analysis.
- The efficacy population: (intention to treat [ITT] population): all randomized subjects who received at least one dose of study drugs were used for descriptive and efficacy analyses.
- The per protocol population: the subset of the ITT subjects who completed study treatment and follow-up, excluding patients with non-virologic failure and non-safety related discontinuation; and who had no major protocol violations.

Study Endpoints

Primary efficacy endpoint

- The proportion of patients in each study group who achieved an SVR at 12 weeks after the last dose of the study medications (SVR12). SVR is defined as serum HCV-RNA below the LLOQ at post-treatment visits. Patients who missed the 12-week post-treatment visit, but had HCV-RNA less than LLOQ at week 24 after end of treatment were excluded from the SVR12 and primary endpoint analysis, but were considered as presumptively having SVR12 in the secondary analysis according to the FDA and EMEA guidelines.[17,18]

Secondary efficacy endpoints

- Proportions of patients who achieved end-of-treatment response (HCV-RNA less than LLOQ at end of treatment), and SVR at 4 and 24 weeks post-treatment.
- Proportion of patients in each treatment group who experienced virologic failure:
  - On-treatment virologic failure (viral breakthrough), defined as more than one log increase in HCV-RNA from post-baseline nadir, or a confirmed increase in HCV-RNA to LLOQ or more if the HCV-RNA had previously decreased to less than LLOQ.
- Virologic relapse, defined as HCV-RNA at or higher than the LLOQ post-treatment in a patient who previously achieved an end-of-treatment response.

Resistance analysis

Resistance analysis was performed by population sequencing on baseline samples and samples at the time of failure for patients exhibiting virologic failure to detect substitutions known to be associated with resistance to NS5A.

We examined possible factors that may predict failure to achieve SVR12. This included use of ribavirin, previous interferon treatment status; and presence or absence of cirrhosis.

Safety endpoints

- Adverse events (AEs) were recorded for all patients who received at least one dose of study medications. AEs were categorized using the Medical Dictionary for Regulatory Activities version 18.1.
- Laboratory abnormalities were graded and presented according to the U.S. National Institutes of Health (Division of AIDS) Table for Grading Severity of Adult Adverse Experiences (1992 and 2003). Laboratory abnormalities were counted starting from visit 3 (first post-baseline dose visit). The ULN/LLN of the laboratory analytes were provided by the central study laboratory.
- Treatment-emergent AEs were any AE occurring after the first dose of study drugs until 30 days after the last dose. Severity and relation to study medication were assessed by the investigator.

Statistical methods

Data are provided for all subjects up to the point of study completion or premature withdrawal, with any subjects excluded highlighted. Data analysis was performed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

For the primary efficacy endpoint analysis: the proportion of patients achieving SVR12, in all patients who started treatment in each study group, was estimated with its 95% confidence intervals. The same analyses were also performed including patients missing SVR12 data but having HCV-RNA less than LLOQ at weeks 4 and 24 post-treatment (SVR24).[17,18] Efficacy was compared between treatment-naïve and treatment-experienced patients, and between patients without and with cirrhosis. Effect of RBV intake on SVR12 was only compared in patients who were randomized to treatment with and without RBV (excluding treatment-experienced patients with cirrhosis). Other subgroups were too small. Per protocol analysis excluded

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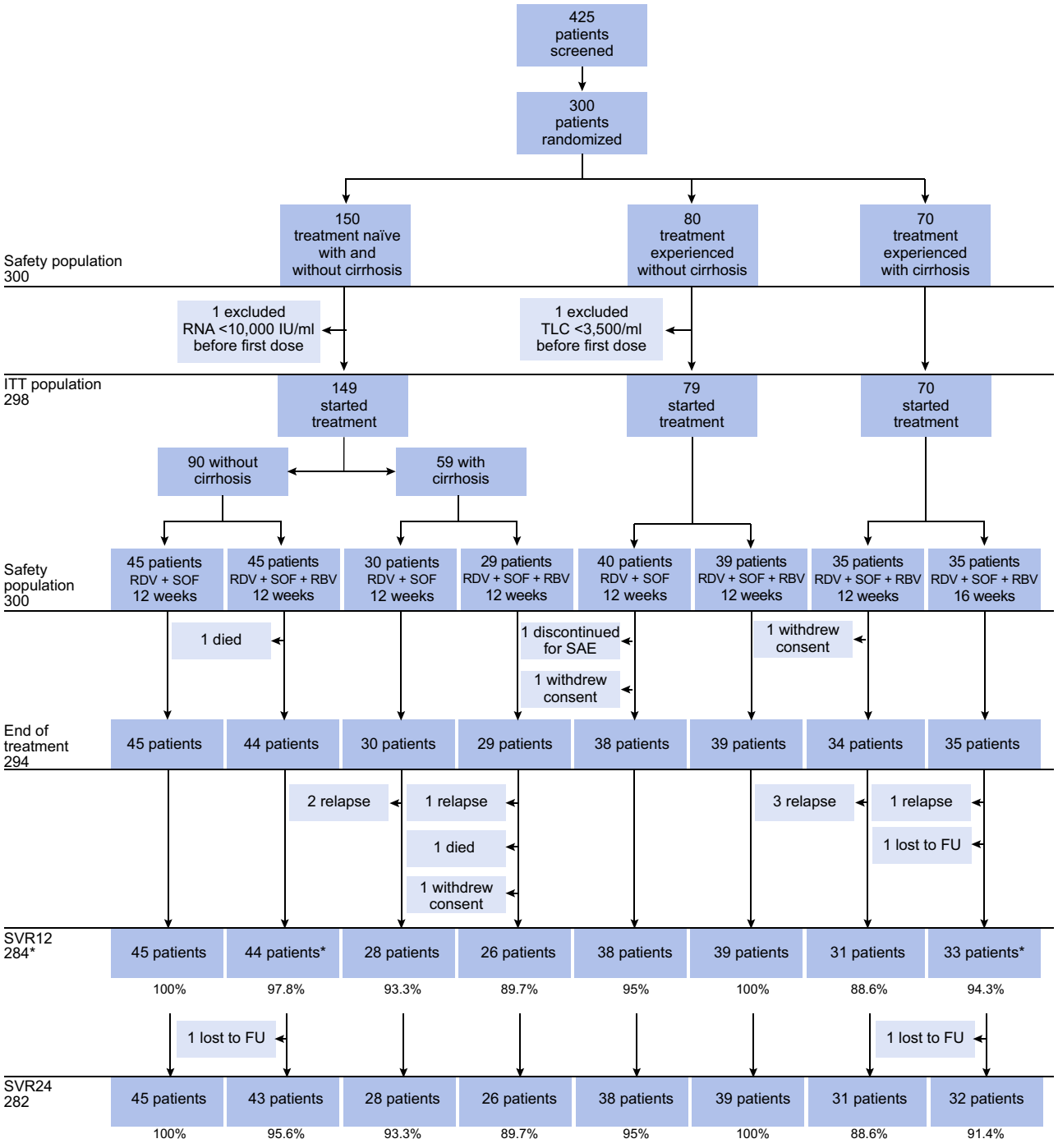

Fig. 2. Patients disposition. FU, follow-up; ITT, intention-to-treat; RBV, ribavirin; RDV, ravidasvir; SAE, serious adverse events; SOF, sofosbuvir; SVR, sustained virologic response; TLC, total leukocyte count.

patients who did not complete treatment and/or follow-up for reasons other than virologic or safety issues. Secondary efficacy endpoints and the incidence of various AEs were also analysed for each treatment group.

To identify pre-treatment or on-treatment characteristics that may affect treatment failure, logistic regression was used.

For further details regarding the materials used, please refer to the CTAT table and supplementary information.

Results

Baseline characteristics

A total of 425 patients were screened, and 300 patients were randomized. Two patients were excluded before the first dose (one because of a decrease in viral load to less than 10,000 IU/ml after randomization, and the other, a patient without cirrhosis, for a decrease in leukocyte count to less than 3,500/mm^3 after randomization but before treatment (Fig. 2). These two

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Table 1. Baseline characteristics and demographic data of studied patients.

Parameter	Group 1 Treatment-naïve with or without cirrhosis(n = 149)	Group 2 Treatment-experienced without cirrhosis(n = 79)	Group 3 Treatment-experienced with cirrhosis (n = 70)	*p value*
Age (years), mean ± SD	46.48 ± 11.56	48.37 ± 9.45	50.39 ± 8.09	**0.03**
Male, n (%)	96 (64.4%)	53 (67.1%)	50 (71.4%)	0.59
BMI, (kg/m^2)	29.06 ± 4.06	29.61 ± 3.54	29.65 ± 4.01	0.46
Laboratory data, mean ± SD				
Bilirubin total (mg/dl)	0.71 ± 0.3	0.68 ± 0.26	0.71 ± 0.7	0.69
ALT (ULN:40 U/L)	69.17 ± 46.5	58.8 ± 46.86	88.94 ± 64.26	**0.002**
AST (ULN:40 U/L)	62.95 ± 38.98	50.92 ± 25.89	82.68 ± 50.19	**<0.001**
INR	1.14 ± 0.15	1.11 ± 0.12	1.12 ± 0.12	0.28
WBC ($\times 10^3/mm^3$)	7.09 ± 2.7	7.25 ± 3.04	6.42 ± 3.43	**0.002**
Hemoglobin (g/dl)	14.67 ± 1.35	15.26 ± 1.61	14.82 ± 1.37	0.008
Platelets ($\times 10^3/mm^3$)	200.13 ± 74.41	214.63 ± 66.64	144.71 ± 56.52	**<0.001**
Creatinine clearance (ml/min)	136.72 ± 55.84	130.42 ± 36.91	139.58 ± 48.84	0.68
HbA1C (%)	5.46 ± 0.82	5.45 ± 0.67	5.85 ± 1.14	0.07
HCV-RNA, median (IU/ml)	260,000	600,000	610,000	**0.001**

The most common co-morbidities were: Diabetes mellitus (17.45%) and hypertension (16.11%).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HbA1c, hemoglobin A1c; INR, international normalized ratio; ULN, upper limit of normal; WBC, white blood cell.

patients were treated outside the trial on a compassionate basis, and both achieved SVR12.

A total of 298 patients started treatment and are included in the ITT population used for the primary efficacy analysis: 149 treatment-naïve patients (Group 1, 90 without and 59 with cirrhosis), and 149 previous treatment failures to IFN-based therapy, including 79 patients without cirrhosis (Group 2) and 70 with cirrhosis (Group 3).

Group 1 (treatment-naïve patients, n = 149) and Group 2 (treatment-experienced without cirrhosis, n = 79) received RDV plus SOF for 12 weeks and were randomized 1:1 to treatment with or without weight-based RBV. The 70 treatment-experienced patients in Group 3, with cirrhosis, all received RDV plus SOF plus weight-based RBV, these Group 3 patients were randomized 1:1 to treatment durations of 12 weeks or 16 weeks (Figs. 1 and 2).

The demographic and baseline characteristics are shown (Table 1). The groups were balanced in most characteristics. Patients with cirrhosis who had previously failed IFN-based therapy (Group 3) were older and had higher aminotransferase levels and lower leukocyte and platelet counts than the other two groups, and HCV-RNA levels were higher among treatment-experienced than treatment-naïve patients (Table 1).

Efficacy

During treatment, two patients withdrew consent (one during week 1 and one during week 3); one patient discontinued because of a non-related serious adverse event (SAE) during the first week of treatment (fractured femur due to a motor vehicle crash), and one patient died during the third week of treatment due to an intracranial hemorrhage considered unrelated to study treatment. At treatment week 4, 94% of the patients had serum HCV-RNA less than LLOQ, and at treatment week 8, all patients had viral load lower than LLOQ (Table S1, Fig. S1). No virologic breakthroughs occurred in any patients. All 294 patients who reached the end of treatment had HCV-RNA less than LLOQ.

Following the end of study treatment, one patient withdrew consent, one was lost to follow-up, and one patient died six weeks after the end of treatment (Table 2, Fig. 2). No virologic failures occurred in patients without cirrhosis. Virologic relapse occurred in seven patients with cirrhosis (2.3% overall, 5.6% of 125 patients with cirrhosis, three treatment-naïve, three treatment-experienced treated for 12 weeks and one treatment-experienced treated for 16 weeks).

Overall, 282 patients achieved SVR12 (94.6%, 95% CI 91.5–96.7). Two patients missed the SVR12 visit but had HCV-RNA less than LLOQ at post-treatment weeks 4 and 24. When these patients' results are imputed as having SVR12 and included,[16,17] 284 patients achieved an SVR12 (95.3%, 95% CI: 92.3–97.2) (Table 2).

The SVR12 rates in different treatment subgroups are shown (Table 2). The SVR12 rate was similar in treatment-naïve and treatment-experienced patients. Among treatment-naïve patients, SVR12 was achieved in 98.9% (95% CI 94.0–99.8) of patients without cirrhosis, and 91.5% (95% CI 81.7–96.3) of patients with cirrhosis. Non-responders to previous IFN-based therapy without cirrhosis had an SVR12 rate of 97.5%, (95% CI 91.2–99.3) and those with cirrhosis who were treated for 16 weeks with RBV had an SVR12 rate of 94.3% (95% CI 81.4–98.4). Treatment-experienced patients with cirrhosis treated with RDV-SOF with RBV for 12 weeks had a higher relapse rate, and an SVR12 rate of 88.6% (95% CI 74.0–95.5) (Table 2, Fig. 2). SVR24 data are shown (Fig. 2 and Tables S1-2), and did not differ from the SVR12 results.

In the per protocol population (the 291 patients who completed therapy and follow-up), the SVR12 rate was 97.6% (95% CI 95.1–98.8) (Table S2).

Addition of RBV to RDV-SOF therapy did not affect the primary treatment outcome (SVR12), and the presence of cirrhosis was the only factor associated with decreased response in this study (Table 3).

Resistance testing on paired baseline and treatment failure samples was done for six of the seven patients who relapsed. None of the baseline samples showed known NS5A resistance-associated substitutions (RASs). At time of relapse, one patient had developed an Y93H substitution, and one patient a M31V substitution. No RASs were detected for the other four patients and therefore their relapse was not related to the emergence of resistance.

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Table 2. Assessment of treatment efficacy among studied patients.

	Treatment naïve (n = 149)				Treatment experienced (n = 149)			
	Without Cirrhosis (n = 90)		With Cirrhosis (n = 59)		Without Cirrhosis (n = 79)		With Cirrhosis (n = 70)	
	RDV+ SOF	RDV+ SOF+ RBV	RDV+ SOF	RDV+ SOF+ RBV	RDV+ SOF	RDV+ SOF+ RBV	RDV+ SOF+ RBV	RDV+ SOF+ RBV
				12 weeks				16 weeks
Number	45	45	30	29	40	39	35	35
During treatment								
Withdrew consent	0	0	0	0	1	0	1	0
Discontinued SAE	0	0	0	0	1	0	0	0
Died	0	1	0	0	0	0	0	0
Number completed treatment	45	44	30	29	38	39	34	35
During Follow-up								
Withdrew consent	0	0	0	1	0	0	0	0
Died	0	0	0	1	0	0	0	0
Lost to FU	0	0	0	0	0	0	0	1
Relapse	0	0	2	1	0	0	3	1
SVR12								
Number SVR12	45	44*	28	26	38	39	31	33*
%	100%	97.8%	93.3%	89.7%	95%	100%	88.6%	94.3%
95% CI	94.3%–100%	88.4%–99.6%	78.7%–98.2%	73.6%–96.4%	83.5%–98.6%	93.5%–100%	74.1%–95.5%	81.4%–98.4%
Number SVR12	89*		54		77		64*	
%	98.9%		91.5%		97.5%		91.4%	
95% CI	94.0%–99.8%		81.7%–96.3%		91.2%–99.3%		82.5%–96.0%	
Number SVR12	143*				141*			
%	96.0%				94.6%			
95% CI	91.5%–98.1%				89.8%–97.3%			
	Without cirrhosis (n = 169)				With cirrhosis (n = 129)			
SVR12								
Number SVR12	166*				118*			
%	98.2%				91.4%			
95% CI	96.2%–100%				86.6%–96.4%			

FU, follow-up; RBV, ribavirin; RDV, ravidasvir; SOF, sofosbuvir; SVR12, sustained virologic response at 12 weeks post-treatment.
* One patient in each group missed the post treatment 12-week visit, but had RNA <LLOQ at post treatment Week 4 and 24, and was considered to have achieved SVR12.

Table 3. Factors that may predict failure to achieve SVR12.

	SVR	*p* value
RBV (randomized groups 1 and 2 only)		
RDV-SOF-RBV	109/113 (96.5%)	1
RDV-SOF without RBV	111/115 (96.5%)	
Previous treatment experience (all patients)		
Treatment-naïve	143/149 (96%)	0.58
Interferon-experienced	141/149 (94.6%)	
Presence of cirrhosis (all patients)		
No cirrhosis	166/169 (98.2%)	**0.006**
With cirrhosis	118/129 (91.5%)	

RBV, ribavirin; RDV, ravidasvir; SOF, sofosbuvir; SVR12, sustained virologic response at 12 weeks post-treatment.

Safety

Overall, regardless of attribution to study treatment, AEs were reported by 69% of patients (Tables 4 and 5, Tables S4,5). Most AEs were mild or moderate in severity, while 10 events (4.9%) were rated severe. The most common AEs (reported by ≥10% of patients) were headache, fatigue, abdominal pain, and pruritus. About half of the reported AEs were judged unlikely to be related or probably not related to the study treatment.

Eleven SAEs occurred in 11 different patients (Table 4), with two of these events leading to discontinuation of study medication: one treatment-experienced patient without cirrhosis had a fractured femur due to a motor vehicle crash during the first week of treatment and discontinued therapy. The other patient was a 46-year-old male, IFN-naïve without cirrhosis, who died in the third week of treatment. Pre-treatment, he was hypertensive on bisoprolol 5 mg once daily and losartan 100 mg once daily, and was randomized to RDV-SOF plus RBV. At baseline, his blood pressure was controlled, and had normal electrocardiogram (ECG) and cardiac examination. On study visits 1, 2 and 3 (screening, baseline, and week 1 visits) he was asymptomatic, his blood pressure was controlled and his biochemical profile was normal. On study visit 4 (week 2) his blood pressure was elevated at 180/110 mmHg. He was referred to cardiology where his bisoprolol dose was increased to 10 mg daily. On that visit, his viral load was 91 IU/ml, and he had no biochemical or hematological abnormalities. Three days later, he had sudden severe headache followed by convulsions, and died on arrival to the emergency room before having brain imaging done. The emergency physician diagnosed the cause of death as due to "intracranial hemorrhage", and this was considered by the study team as probably not related to study medications. The patient was not receiving anti-coagulants or antiplatelets, and his INR and platelet count did not change with treatment until his last study visit. There are no drug-drug interactions between SOF and bisoprolol or losartan, and none is currently known with RDV.

Other SAEs included abdominal pain, myocardial infarction, hearing disorder (in a 51-year-old male who developed moderate sensory hearing loss that did not resolve until the end of follow-up), gastrointestinal bleeding (non-steroidal anti-inflammatory induced gastro-duodenal bleeding in a 61-year-old male with cirrhosis), arrhythmia, vomiting, hypertension, and retinal detachment. All but two of the SAEs were judged

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Table 4. Assessment of treatment safety among studied patients.

	Group 1 Treatment-naïve with and without cirrhosis (n = 149)	Group 2 Treatment-experienced without cirrhosis (n = 79)	Group 3 Treatment-experienced with cirrhosis (n = 70)	Total (N = 298)
Any adverse events	97 (65%)	55 (70%)	52 (74%)	204 (69%)
Most common events occurring in 10% of patients overall				
Headache	36 (24%)	36 (46%)	19 (27%)	91 (31%)
Fatigue	22 (15%)	14 (18%)	18 (26%)	54 (18%)
Abdominal pain	13 (9%)	9 (11%)	8 (11%)	30 (10%)
Pruritus	13 (9%)	14 (18%)	2 (3%)	29 (10%)
Common events number occurring in 3% of patients overall				
Naso-pharyngitis	7 (5%)	7 (9%)	1 (1%)	15 (5%)
Constipation	6 (4%)	4 (5%)	3 (4%)	13 (4%)
Diarrhoea	5 (3%)	4 (5%)	3 (4%)	12 (4%)
Bone pain	3 (2%)	2 (3%)	6 (9%)	11 (4%)
Arthralgia	6 (4%)	3 (4%)	1 (1%)	10 (3%)
Serious adverse events	4 (3%)	2 (3%)	5 (7%)	11 (4%)
Death	2	0	0	2
Bilirubin elevation				
Grade 1-2	50 (34%)	25 (32%)	42 (60%)	117 (39%)
Grade 3-4	2 (1%)	0	0	2 (0.7%)
Hemoglobin decrease				
Grade 1	5 (3%)	2 (3%)	2 (3%)	9 (3%)
Grade 2	1 (1%)	0	0	1 (0.3%)

Table 5. Hemoglobin decrease in treatment subgroups according to RBV intake.

	Group 1				Group 2		Group 3		Overall (N = 298)
	Treatment-Naïve without Cirrhosis		Treatment-Naïve with Cirrhosis		Treatment-Experienced without Cirrhosis		Treatment-Experienced with Cirrhosis		
	RDV +SOF n = 45	RDV+SOF +RBV n = 45	RDV +SOF n = 30	RDV +SOF +RBV n = 29	RDV +SOF n = 40	RDV +SOF +RBV n = 39	RDV +SOF +RBV (12 weeks) n = 35	RDV+SOF +RBV (16 weeks) n = 35	
Hemoglobin decrease (grade 1-2)	0	3 (6.7%)	0	4 (13.8%)	1 (2.5%)	1 (2.6%)	1 (2.9%)	0	10 (3.4%)

Without RBV (1 of 115 patients, 0.9%) *vs.* with RBV (9 of 185 patients, 4.9%) ($p = 0.06$). Among patients receiving RBV: without cirrhosis (4 of 85 patients, 4.7%) *vs.* with cirrhosis (5 of 100 patients, 5%) ($p = 0.93$).
RBV, ribavirin; RDV, ravidasvir; SOF, sofosbuvir.

by the site investigator to be unlikely related to the study medications. The SAEs that were considered possibly related to study treatment were the case of hearing impairment, and a transient episode of symptomatic bradycardia in an IFN-experienced patient with cirrhosis treated with RDV-SOF plus RBV for 12 weeks. The patient was not receiving amiodarone, and the bradycardia resolved without sequelae. In addition to the patient who died due to an intracranial hemorrhage in week 3, a second mortality occurred in a treatment-naïve 60-year-old female with cirrhosis (Child class A, CTP score 6, MELD score 12.5) who was randomized to RDV-SOF plus RBV for 12 weeks, completed treatment and achieved SVR4. Before the 8-week post-treatment visit, this patient decompensated (developed ascites and encephalopathy) and she missed the subsequent visit. She died before admission to hospital, but her ultrasound on an ER visit showed ascites and a large focal lesion in the right lobe which could have been a hepatocellular carcinoma. Baseline ultrasonography examination did not show focal lesions in the liver, she had not developed manifestations of hepatic decompensation prior to inclusion, and did not decompensate during treatment. She died before having further investigations to confirm the nature of the focal lesion, before the post-treatment 12-week visit. The possibility of the focal lesion being a hepatocellular carcinoma and its relation to treatment medication is not settled. Both mortalities are considered unlikely to be related to study treatment.

No patient experienced grade 2 or higher aminotransferase elevation, and the most frequent laboratory abnormalities were grade 1 gamma-glutamyl-transferase elevation (58%), followed by grade 1 total bilirubin elevation (35%), and grade 1 alkaline phosphatase elevation (33%) (Table S3). One patient had grade 3 (>2.5 mg/dl) and one patient had grade 4 (>5 mg/dl) total bilirubin elevation, both lasting for no more than two study visits, which resolved without discontinuing treatment. Bilirubin elevations were not associated with aminotransferase elevations; and toxicity criteria (aminotransferase elevation >3 times ULN with bilirubin elevation >2 times ULN) were not met in any patient.

Grade 1 and 2 hemoglobin decrease occurred in 10 patients overall (3.4%) (Tables 4 and 5, Table S4), involving one patient not receiving RBV (0.9%) and nine patients receiving RBV (4.9%, p = 0.06). Hemoglobin decrease in patients receiving RBV was not more common in patients with cirrhosis (Table 5). RBV dose was reduced in the nine affected patients. No patient developed hemoglobin below 8.5 gm/dl. Other AEs were not more frequent in patients receiving RBV (Table S5).

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Discussion

HCV-GT4 infects 12 to 15 million HCV patients worldwide. Most patients with HCV-GT4 infection reside in limited resource countries: mainly in Egypt, the Middle East, and sub-Saharan Africa.[19] In most of these countries, access to new DAA agents is limited, and the need still exists for affordable effective treatments. HCV-GT4 has been under-represented in clinical trials with direct antivirals, and approval of therapies for HCV-GT4 have been based on trials involving relatively small numbers of HCV-G4 patients.[20–28]

This study is one of the largest randomized trials of IFN-free DAA treatment conducted with HCV-GT4 patients. Study treatment included generic SOF produced by a local company (Pharco Pharmaceuticals) and a novel pan-genotypic NS5A inhibitor (RDV) discovered by a US based company (Presideo Parmaceuticals, Ca, USA), which is being co-developed with Pharco Pharmaceuticals. This study is the first clinical trial evaluating this combination in patients with HCV and in patients with HCV-GT4.

RDV is a pan-genotypic anti-HCV NS5A inhibitor with a favorable pharmacokinetic profile, rapid plasma concentrations, and high 24-h trough concentrations, allowing for continuous HCV inhibitory drug concentrations with once daily oral dosing. RDV achieves steady-state with the first dose, and from day 2 onward, peak and trough levels remain constant without evidence for either subsequent drug accumulation or drug induced clearance.[12]

In phase I trials, RDV proved to be well tolerated and efficacious with no appreciable pattern of treatment-related AEs.[13] Observed resistance substitution did not subsequently increase during continued RDV monotherapy (days 2-3), suggesting that its concentrations were sufficient to suppress single substitution variants during early treatment.[14] RDV was studied in combination with deleobuvir (non-nucleoside NS5B polymerase inhibitor) and faldaprevir (NS3-NS4 protease inhibitor) to treat HCV-GT1 patients.[13] An SVR was achieved in 92% of patients.

In this multicenter study that included patients with HCV-GT4 treated with RDV plus SOF with or without RBV, 95.3% of all patients achieved an SVR, including patients with cirrhosis, and those who had previously failed IFN-based therapy. Of 14 patients who did not achieve the primary endpoint of an SVR12, only seven were due to virologic failures (2.3%) and seven were not efficacy related (2.3%). There were no virologic failures in patients without cirrhosis.

With IFN-based regimens, SVR was related to several patient and treatment characteristics, including body mass index, stage of fibrosis, baseline viral load, an early virologic response, previous failure of IFN-based therapy,[29] treatment duration and use of RBV.[30] In this study, BMI, baseline viral load, previous interferon experience, and the use of RBV did not affect treatment efficacy. Only the presence of cirrhosis was associated with lower SVR12 rates, especially in patients treated for 12 weeks.

No on-treatment virologic breakthroughs occurred in this study. Patients without cirrhosis did not experience virologic relapses. All virologic failures occurred in patients with cirrhosis, and the presence of cirrhosis significantly reduced SVR rates (91.5% with cirrhosis *vs*. 98.2% without cirrhosis, $p = 0.006$).

Clinical trials with SOF based therapy in patients with HCV-GT4 produced similarly high rates of SVR when combined with peg-IFN and RBV.[20] With an IFN-free SOF-RBV combination, lower SVR rates of 68%–77% were achieved when used for a duration of 12 weeks and 90%–93% for 24 weeks.[21,22] In a real-life report that included 14,409 HCV-GT4 patients treated by SOF plus RBV or SOF plus peg-IFN and RBV, SVR rates ranged between 78.7% and 94%.[31] SOF-ledipasvir combination in HCV-GT4 resulted in SVR rates of 95% in a small clinical trial that included 20 patients,[23] 91%-95% in treatment-experienced and treatment-naïve patients in a French multicenter trial,[24] and 90% to 100% in 254 treatment-naïve and experienced patients without or with cirrhosis treated for 8 or 12 weeks in a multicenter trial in Egypt. [32] The combination of SOF-velpatasvir, on the other hand, was associated with a 100% SVR rate among 116 HCV-GT4 patients in the Astral-1 trial, regardless of previous treatment history or the presence of cirrhosis. [33] NS3-NS4 protease inhibitors in combination with SOF or NS5A inhibitors have also proved very effective in treatment of HCV-G4 in similar patients in Egypt: treatment-naïve and interferon-experienced patients with or without cirrhosis had SVR12 results exceeding 95% when treated with SOF plus simeprevir,[25] and with ritonavir-boosted pariteprevir in combination with ombitasvir plus ribavirin. [26] The combination of elbasvir-grazoprevir given for 12 weeks without RBV was associated with SVR rates of 95%–100% in treatment-naïve mono-infected, and HIV co-infected, HCV-G4 patients,[34,35] but with lower response in treatment-experienced patients (that only improved with the addition of RBV and prolonging treatment duration).[36] The SVR rates in this trial using IFN-free RDV plus SOF with or without RBV in treatment-naïve and experienced patients with and without cirrhosis were similarly high.

The seven patients who had virologic failure (post-treatment relapse), all had cirrhosis, and none of the six for whom resistance-related sequencing was available had baseline NS5A substitutions known to decrease treatment responses. Only two had individual NS5A RASs at the time of relapse.

RDV plus SOF therapy was well tolerated by the patients with and without cirrhosis enrolled in this study. Most AEs were mild and considered to be unlikely related to study drugs, similar to other direct antiviral combination therapies.[37] SAEs occurred in 3.7% of the study group, and only two SAEs resulted in treatment discontinuation (<1%). We did not include a placebo arm in the study, and whether the safety pattern of RDV is similar to placebo cannot be concluded, as the only trial that compared RDV to placebo was a short phase I trial.[12] Symptomatic bradycardia has been reported as an occasional AE with SOF treatment, with cirrhosis as a risk factor for its occurrence.[38] The case of bradycardia in this study was considered treatment-related, and resolved without sequelae. The patient with cirrhosis who died after eight weeks of the end of treatment had evidence of hepatic decompensation and an undiagnosed mass in the liver, most probably an hepatocellular carcinoma (HCC). The association of HCC development to DAA therapy is still questionable. Some reports suggest increased risk of tumor recurrence and/or *de novo* occurrence in patients with cirrhosis,[39,40] with reports of increased invasiveness and aggressiveness of these tumors.[41] Other reports suggest that the incidence of HCC is either not increased or is decreased.[42,43] The ongoing debate makes it difficult in this case to suggest a relationship to treatment, and this remains a possibility.

Our study and its results are limited to patients with HCV-GT4, who have no cirrhosis or have compensated cirrhosis. Although HCV-GT4 affects only around 12%–15% of chronic HCV patients worldwide, it is concentrated in geographic areas with limited resources and limited access to treatment, where affordable effective therapies are urgently needed. Furthermore,

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the combination of RDV plus SOF with or without RBV is currently being studied in patients with and without cirrhosis who are infected with diverse HCV genotypes with or without HIV coinfection (ClinicalTrials.gov Identifier: NCT02961426), supporting the potential emergence of RDV plus SOF therapy as a new effective pan-genotypic HCV therapy. We did not subtype patients with HCV-G4, and cannot comment on outcome in different HCV-G4 subtypes, and no *in vitro* data are available for RDV efficacy on HCV-G4 subtypes other than subtype 4a.[44] However, HCV-G4a is the predominant subtype in Egypt, where more than 87% of HCV-G4 infections are due to subtype 4a.[45] We included only patients with compensated Child-A cirrhosis, and the safety and efficacy of this combination in patients with decompensated cirrhosis will need further studies. Also, our results are limited to patients who have failed previous IFN-based therapy, and cannot be generalized to patients who have failed DAA regimens.

While there are several very effective treatments for HCV-G4, the combination of SOF-RDV has the potential to be a very cheap option both in Egypt (with the availability of generic SOF, and with RDV developed by a local company that is promising a very cheap local market price) and to all low and middle income countries (LMICs) through its development with Drugs for Neglected Diseases Initiative, who are also promising to make medications for HCV affordable to all LMICs (including this combination if ongoing trials in other genotypes also prove effective). They have announced that the global target price would be less than US$300 for 12 weeks' treatment.[46]

In conclusion, RDV plus SOF is a promising new once daily oral treatment that was well tolerated in a large group of HCV-G4 patients, with high rates of SVR in patients with and without cirrhosis.

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Conflict of interest

Gamal Esmat: Received grants/research supports or speaker's honoraria from: Abbvie, BMS, Gilead, Glaxo, Janssen, MSD, Pharco, and Roche. Maissa El Raziky Received grants/research supports from: BMS, Eipico, Gilead, Janssen, MSD, Pharco, and Roche. Sherine Helmy: Owns Pharco Stock. Hanaa Abdel-Maguid: Was Pharco employee during the study. Richard Colonno, Nathaniel Brown, Eric Ruby, Pamela Vig: employees of Presidio Pharmaceuticals. Imam Waked: Received grants/research supports or speaker's honoraria from: Abbvie, Gilead, Janssen, Pharco, Mylan, Onxio, and Roche. TE, AG, MMA, HG, AS, MKA, NA, MAH, ON: Nothing to declare.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

GE, ME, and IW designed the study. GE, IW, ME, TE, AG, AS, MMA, HG, MKA, NA: performed the study, including patient recruitment, treatment, and follow-up of patients, data collection and interpretation, and preparation and critical review of the report. MA, ON did the laboratory work. SH, HA, RC, NB, ER: participated in the study design, protocol authorship, statistical analysis plan, and international regulatory documentation. HA and PV supervised the external clinical monitoring of the study. HA, RC and SH: provided the study medications. TE, and IW wrote the manuscript. All authors contributed to the final version of the manuscript.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jhep.2017.09.006.

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